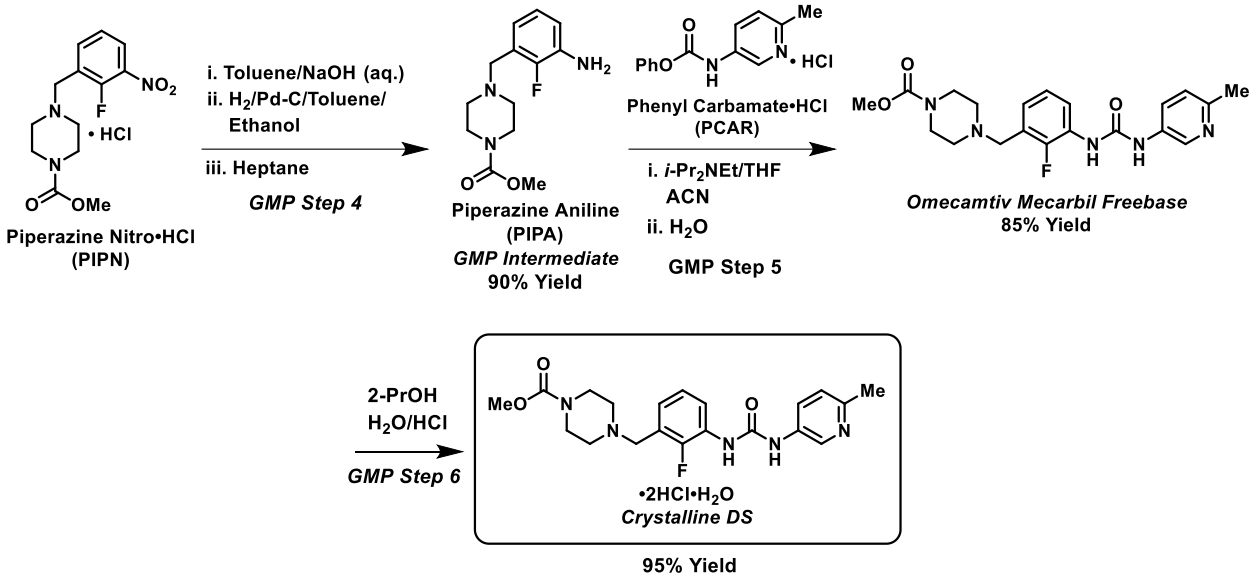
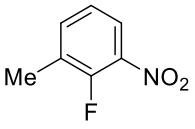


[0008] The processes for preparing OM disclosed in the '270 WO and '231 WO publications use FNT as a starting material. FNT is a raw material that is currently manufactured from 2-fluorotoluene using a short synthetic sequence. A drawback to this process is a requisite fractional distillation step of the mixture of isomers generated in order to afford the desired regioisomer, 2-fluoro-3-nitro-toluene, in acceptable purity, with no greater than 0.5% of any other isomers, as measured by gas chromatography. Moreover, the desired regioisomer of FNT is obtained by the process is less than 10% yield.

[0009] In view of the foregoing, there is a need for a reproducible, efficient preparation of FNT and other compounds useful for the manufacturing of OM.

SUMMARY



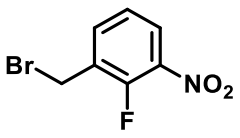
[0010] The disclosure provides processes for synthesizing 2-fluoro-3-nitrotoluene (FNT) comprising (a) admixing 2-fluorotoluene with one or more bases and a boronation reagent to form a boronic acid and (b) admixing the resulting boronic acid with iron nitrate or a hydrate thereof to form FNT.

[0010a] In one aspect, the disclosure provides a process for synthesizing 2-fluoro-3-nitrotoluene ("FNT") comprising (a) admixing 2-fluorotoluene with one or more bases and a boronation reagent to form a boronic acid; and (b) admixing the resulting boronic acid with iron nitrate or a hydrate thereof to form the FNT.

[0011] The disclosure also provides processes for synthesizing FNT comprising (a) admixing 2-fluorotoluene with one or more bases and a boronation reagent to form a boronic acid and (b) admixing the resulting boronic acid with nitric acid to form FNT.

[0011a] In another aspect, the disclosure provides a process for synthesizing 2-fluoro-3-nitrotoluene ("FNT") comprising (a) admixing 2-fluorotoluene with one or more bases and a boronation reagent to form a boronic acid; and (b) admixing the resulting boronic acid with nitric acid to form the FNT.

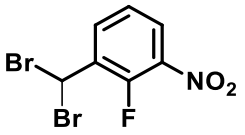
[0012] In yet another aspect, the disclosure further provides a process for synthesizing 1-(bromomethyl)-2-fluoro-3-nitrobenzene



(FNB)

comprising

(a) admixing 2-fluoro-3-nitrotoluene (FNT) with a bromination agent in the presence of blue LED light to

form a mixture of FNB and 1-(dibromomethyl)-2-fluoro-3-nitrobenzene  ($FNBr_2$);

(b) admixing the FNB/$FNBr_2$ mixture with a dialkyl phosphite to form FNB; and

(c) optionally purifying FNB formed in step (b) by (i) washing the FNB with a dialkylphosphite and a trialkylamine, or (ii) extracting the FNB with an organic solvent and washing with aqueous base.

[0012a] In one aspect, the disclosure provides a process for preparing omecamtiv mecarbil or a salt thereof, a hydrate thereof, or a salt hydrate thereof, the process comprising the process as disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 shows the diagram for the set up for the flow chemistry preparation of LDA in Example 2-1.

[0014] Figure 2 shows the diagram for the set up for the flow chemistry borylation of 2-fluorotoluene in Example 2-1.

[0015] Figure 3 provides a diagram for the setup of the flow chemistry preparation of PIPN HBr from FNT as described in Example 3.

[0016] Figure 4 shows a graph depicting the concentration data summary for the collected fractions for the crude PIPN stream from the flow chemistry preparation of PIPN HBr from FNT as described in Example 3.

DETAILED DESCRIPTION

[0017] Provided herein are processes for preparing FNT and other compounds useful in the manufacturing of OM and salts and hydrates thereof (e.g., OM dihydrochloride monohydrate). In some embodiments, the disclosure provides processes for manufacturing starting materials and intermediate compounds used in commercial processes for preparing OM dihydrochloride monohydrate.

[0018] In some embodiments, the disclosed processes are conducted in batch mode (i.e., "batch chemistry"). In other embodiments, the disclosed processes are conducted using continuous manufacturing processes (i.e., "flow chemistry" or "continuous chemistry"). As used herein, continuous manufacturing refers to an integrated system of unit operations, with constant flow (steady or periodic). The disclosed processes utilizing continuous chemistry can provide the production of gram to metric ton quantities of active pharmaceutical ingredients (APIs). In still other instances, the disclosed processes comprise a combination of steps that are conducted using batch chemistry and of steps conducted using continuous chemistry.

Processes for Synthesizing FNT

[0019] The disclosure provides processes for preparing FNT. In some embodiments, the processes for synthesizing FNT comprise (a) admixing 2-fluorotoluene with one or more bases and a boronation reagent to form a boronic acid and (b) admixing the resulting boronic acid with iron nitrate or a hydrate thereof to form FNT. Alternatively, in some embodiments, the disclosure provides processes for preparing FNT, wherein step (a) is as described above and step (b) is admixing the resulting boronic acid with nitric acid to form FNT. Illustrative embodiments of the process are shown in Scheme 4A and 4B, wherein the process depicted in Scheme 4A